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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/523,886	03/13/2000	David J. Grdina	P-01904US1	6435

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Fulbright & Jaworski LLP
Suite 2400
600 Congress Avenue
Austin, TX 78701

EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/19/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/523,886	Grdina et al.
Examiner	**Art Unit**
Shin-Lin Chen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 17, 2003*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3-7, 9-13, and 23-33* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3-7, 9-13, and 23-33* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☒ Interview Summary (PTO-413) Paper No(s). *20*
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3-17-03 has been entered.

Applicants' amendment filed 2-7-03 has been entered. Claims 1, 9-13, 23 and 30-33 have been amended. Claim 8 has been canceled. Claims 1, 3-7, 9-13 and 23-33 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 3-7, 9-13 and 23-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting or reducing the number of metastases in lung by administering WR-2721 at a concentration of 50mg/kg to 100mg/kg to an animal, does not reasonably provide enablement for reducing the number or inhibiting metastases in tissues other than lung or preventing metastases by administering any aminoalkylphosphorothioate or active metabolite thereof, or reducing the number of metastases by administering WR-2721 at a

concentration of 10mg/kg to less than 50mg/kg or at a concentration between 100mg/kg to 150mg/kg to an animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1, 3-7, 9-13, 23-29, 32 and 33 are directed to a method for reducing the number of metastases in an animal having a primary tumor, such as a sarcoma or a carcinoma, by administering to said animal an aminoalkylphosphorothioate or active metabolite thereof at a concentration of 10mg/kg to 150mg/kg. Claim 6 specifies the animal is a human. Claim 10 specifies the active derivative is the disulfide form. Claims 12 and 13 specify the route of administration is intravenous, intraperitoneal etc., and the aminoalkylphosphorothioate or active metabolite thereof is formulated into solutions, suspensions, tablets etc, respectively. Claims 25-29 specify further monitoring the ability of the dose of the aminoalkylphosphorothioate or active metabolite to reduce metastases via measuring the activity of matrix metalloproteinase (MMP), such as MMP-2 or MMP-9, the stimulation of angiostatin, or the stimulation of MnSOD gene expression. Claims 32 and 33 specify the aminoalkylphosphorothioate is WR-2721 and WR-1065, respectively. Claims 30 and 31 are directed to a method for inhibiting or preventing metastases in an animal having a primary tumor by administering to said animal an aminoalkylphosphorothioate or active metabolite thereof.

The claims encompass using any aminoalkylphosphorothioate compound at a concentration of 10mg/kg to 150mg/kg and its active metabolite including the list of compounds

disclosed in the specification to reduce the number of metastases, to inhibit metastases, at any location or to prevent metastases in an animal (page 13). The specification only discloses inhibition of metastases of lung by using WR-2721, i.e. amifostine, at a concentration of 50mg/kg to 100mg/kg in C3Hf/Kam mice, which have been injected with sarcoma or adenocarcinoma tumor cells.

The specification fails to provide adequate guidance and evidence for reducing the number metastases or inhibiting metastases in tissues other than lung by administering any aminoalkylphosphorothioate or active metabolite thereof, or reducing the number of metastases by administering WR-2721 at a concentration of 10mg/kg to less than 50mg/kg or at a concentration between 100mg/kg to 150mg/kg to an animal. The specification only discloses inhibition of metastases of lung by using WR-2721, i.e. amifostine, at a concentration of 50mg/kg to 100mg/kg. The occurrences of metastases result from various types of tumors at different locations or tissues in an animal rely on different mechanisms and pathobiologies. There is no evidence of record that WR-2721 or any other aminoalkylphosphorothioate can reduce the number of metastases or inhibit metastases of tissues or locations other than lung in an animal. Kanclerz et al., 1988 (exhibit D) states that "treatment with a single dose of WR-2721 (0.4g/kg) promoted lung metastases but exerted a suppressive effect on lymph node tumors. When the radioprotector was given in fractioned schedules in three different doses (0.05g/kg, 0.1g/kg and 0.2g/kg for 10 consecutive days) a slight enhancement of lung metastases and suppression of extrapulmonary metastases was observed". Kanclerz also reports that

misonidazole and SR-2508 promote lung metastases formation (e.g. abstract, p. 313, right column). Figure 4 of Kanclerz shows that 0.05g/kg (50mg/kg) and 0.1g/kg (100mg/kg) of WR-2721 do not inhibit metastases at sacral and paraaortic nodes and mediastinum in mice, and only significantly inhibit metastases in adrenals of mice. Therefore, doses and schedules of a compound administered to a subject and the type of tumors and location of metastases are important factors in determining the effect of said compound on metastases. It would be unpredictable at the time of the invention whether any aminoalkylphosphorothioate or its active metabolite can reduce the number of metastases or inhibit metastases at locations other than lung in an animal. Further, the prior art only discloses inhibition of metastases in the lung by using WR-2721 but not by using any other aminoalkylphosphorothioate. It also would be unpredictable at the time of the invention whether any aminoalkylphosphorothioate or its active metabolite other than WR-2721 can reduce the number of metastases or inhibit metastases at any location in an animal.

The specification only discloses inhibition of metastases of lung by using WR-2721 at a concentration of 50mg/kg to 100mg/kg. A dose of WR-2721 at 200mg/kg does not inhibit spontaneous Sa-NH metastases formation (see Figure 1 of the present invention). Kanclerz reports single dose of WR-2721 of 0.4g/kg promotes lung metastases, however, Milas et al., 1984 (IDS-C51) states that single dose of 400mg/kg WR-2721 greatly reduces radiation and CY-induced enhancement of metastases in the lung of mice. The specification fails to provide adequate guidance and evidence whether WR-2721 at a concentration of 10mg/kg to less than

50mg/kg or at a concentration between 100mg/kg to 150mg/kg can reduce the number of metastases at various locations in an animal. In view of the contradiction of the data regarding WR-2721 at a concentration of 400mg/kg (Kanclerz and Milas) and the lack of evidence of the activity of WR-2721 at a concentration of 10mg/kg to less than 50mg/kg or at a concentration between 100mg/kg to 150mg/kg, it would be unpredictable at the time of the invention whether WR-2721 at said concentration range can reduce the number of metastases at various locations in an animal. One skilled in the art the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

The specification also fails to provide adequate guidance and evidence for prevention of metastases of various tumors *in vivo* by using any aminoalkylphosphorothioate and active metabolites thereof, such as WR-2721. The specification injects WR-2721 **after** the injection of tumor cells into mice and Tables 1 and 2 show occurrence of spontaneous metastases and incidence of metastases for Sa-NH, MCak, and OCa tumors in mice. Preventing metastases in an animal means administration of the drug **before** infection or introduction of pathogen to said animal and said administration of the drug prevent the occurrence of metastases in said animal. In view of such, the specification fails to provide enabling evidence that WR-2721 or any aminoalkylphosphorothioate at a concentration of 10mg/kg to 150mg/kg can prevent metastases at various locations in an animal.

Claim 6 specify the animal is a human. The biological environment *in vitro* differ dramatically from the biological environment *in vivo*, and different organisms differ from each

other physically and physiologically. Gura (Science, Vol. 278, p. 1041-1042, 1997) reports "The fundamental problem in drug discovery for cancer is that the (animal) model systems are not predictive at all" and "The animals apparently do not handle the drugs exactly the way the human body does. And attempts to use human cells in culture don't seem to be faring any better, partly because cell culture provides no information about whether a drug will make it to the tumor site" (e.g. p. 1041, first column). Similarly, the effect of WR-2721 at a concentration of 50mg/kg to 100mg/kg in reducing the number of metastases of lung in mice can not be extrapolated into the effect of WR-2721 in a human. In view of such, and the contradiction of the data regarding WR-2721 at a concentration of 400mg/kg (Kanclerz and Milas) and the unpredictability whether WR-2721 at cited concentration range can reduce the number of metastases at various locations in an animal as discussed above, one skilled in the art the time of the invention would not know how to use various concentration of any aminoalkylphosphorothioate or active metabolite thereof to practice over the full scope of the invention claimed.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples given and scarcity of guidance in the specification, and the unpredictable nature of the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.